II. Remarks

A. Amendments to the Claims and Formal Matters

Claims 62, 66-71 and 75-82 and 87-94 are pending and under active consideration in the application. Claims 87 and 90-92 have been withdrawn by the Examiner. Claim 88 is amended. Claim 94 is canceled without prejudice to pursuing this claim in one or more continuing applications. Upon entry of these amendments, claims 62, 66-71, 75-82 and 87-93 will be pending with claims 62, 66-71, 75-82, 88-89 and 93 under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

Claim 88 is amended to delete reference to claim 87, which has been withdrawn by the Examiner.

Applicant respectfully submits that no new matter has been added by the amendments.

B. Claim Objections

At page 3 of the Office Action, the Examiner has objected to claims 88 and 89 because "the claims have not been amended to recite the elected species of the invention, multiple sclerosis as an autoimmune disease; and encompasses non-elected subject matter, i.e. cancer, viral disease and a broad variety of autoimmune diseases.

Applicant respectfully submits that claims 88 and 89 are proper. The Examiner, pursuant to the interview of October 27, 2005 with Applicant's representative, withdrew the restriction requirement dated October 6, 2005. Pursuant to that same interview, Applicant elected with traverse the species autoimmune disease and multiple sclerosis, to which the claims shall be restricted if no generic claim is finally held to be allowable. Because claims 88 and 89 are generic to and read on the elected species, Applicant respectfully requests withdrawal of the objections.

C. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn

a. Claims 62, 66-71, 75-82 and 93

At pages 3-5 of the Office Action, the Examiner maintained the rejection of claims 62, 66-71 and 75-82 under 35 U.S.C. §112 for an alleged lack of enablement and further applied the rejection to new claim 93. The Examiner based this rejection on his allegation that "other type I IFN receptors cannot be excluded, and hence encompass isolated and mutated polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms." Moreover, according to the Examiner, "the claims allow for the addition of any of numerous amino acid to various regions of SEQ ID NO: 2 that can introduce substantial variation, affecting binding of IFNβ." Applicant hereby reiterates and incorporates by reference all of the arguments made in response to this rejection made during prosecution of this application to date.

Applicant respectfully disagrees with the Examiner and respectfully submits that the full scope of claims 62, 66-71, 75-82 and 93 is enabled by the present disclosure. As a preliminary matter, Applicant reminds the Examiner that claim 62 and dependent claims 66-71, 75-82 and 93 each contain limitations that require: (1) that the polypeptide comprises the sequence of SEQ ID NO:2; (2) that the polypeptide contains alanine substitutions at positions 78 and 100 of the extracellular domain; and (3) that said substitutions synergistically increase the affinity of the claimed polypeptide for IFN-β compared to the wild type polypeptide. Accordingly, the scope of the claim does not extend to polypeptides which do not retain the synergistic increase in affinity for IFN-β. Moreover, and contrary to the Examiner's assertions, the pending claims simply do not encompass the "change, deletion, or addition" of "any of numerous amino acids to various regions of SEQ ID NO: 2 that can introduce substantial variation, affecting binding of IFNβ." Similarly, Examiner's citation of Bowie is entirely irrelevant to an analysis of whether the full scope of the claims is enabled by the instant disclosure. Bowie is cited by the Examiner to support the instant rejection; however, Bowie is directed to the determination of a protein's function from its structure which clearly has no place in an enablement analysis wherein the function of the claimed polypeptide is known, as is the case here.

A polypeptide consisting of SEQ ID NO:2 with the claimed mutations is demonstrated, as a working embodiment, to exhibit increased affinity for IFN-β. While

the pending claims cover, e.g., fusion proteins comprising SEQ ID NO:2 with the claimed alanine substitutions, such fusion proteins can be created without undue experimentation by one of ordinary skill in the art and would not be expected to interfere with the synergistically increased affinity for IFN-β relative to the wild type protein. Indeed, the "membrane bound, cytoplasmic and soluble forms" of IFNAR2 cited by the Examiner, each of which has been demonstrated by the prior art to bind IFN-β through the extracellular domain, provides evidence that polypeptides comprising SEQ ID NO: 2 are capable of binding IFN-β regardless of the presence or absence of amino acids in addition to SEQ ID NO: 2.

Finally, the specification describes binding assays by which one of ordinary skill in the art can identify members of the genus which exhibit synergistically enhanced affinity for IFN-β. *See, e.g.*, specification, paragraph [0090].

Accordingly, Applicant respectfully submits that one of ordinary skill in the art would, in view of the disclosure provided by the Applicant, and of common general knowledge at the time the present Application was filed, identify members of the claimed genus of polypeptides exhibiting the claimed synergistically enhanced affinity for IFN-β. Therefore, Applicant requests that the Examiner withdraw the rejection of claims 62, 66-71, 75-82 and 93 for lack of enablement.

b. Claims 88, 89 and 94

At pages 5-7 of the Office Action, the Examiner applied the previous rejection of claims 83 and 85 (now canceled) under 35 U.S.C. §112 for an alleged lack of enablement to new claims 88, 89 and 94 for the reasons of record. Applicant herein cancels claim 94, rendering the rejection thereto moot. With regard to the remaining rejections, Applicant respectfully traverses.

The Examiner first alleges that "the prior art teaches that the role and contribution of IFNAR2, to ligand binding and signal transduction remains unknown, and that soluble IFNAR2a has been found to inhibit the functional activity of type I interferon." Applicant directs the Examiner's attention to the specification, at page 7, paragraphs [0029]-[0030], which teaches that the use of the claimed polypeptides in modulating the immune response is to act as **carrier** proteins for IFN-β. Where the claimed

polypeptides are administered alone, they form a complex *in vivo* with endogenous IFN-β and thus stabilize and enhance the activity of endogenous IFNβ. *See* specification, page 9, paragraph [0036]. Where the claimed polypeptides are administered covalently bound to IFN-β, the complex exhibits improved stability, enhanced potency and/or prolonged pharmacokinetics *in vivo* compared to administration of free IFN-β. *See ibid.* Accordingly, the role/contribution of IFNAR2 to signal transduction is irrelevant, although, contrary to Examiner's allegation such role is known. With regard to the contribution of IFNAR2 to ligand binding, the instant specification discloses at page 2, paragraph [0006] that IFNAR2 alone is able to bind IFN-α and IFN-β, although the only pertinent point with regard to the instant claims is the demonstrated ability of IFNAR2 and the claimed polypeptides to bind IFN-β. The activity of type I interferons in modulation of the immune system is known and it is known that type I interferons act through a cell surface receptor complex to induce such a biological effect. *See* specification, pages 1-2, paragraphs [0005]-[0006]. Additionally, intrathecal administration of the type I interferon IFN-β has been demonstrated to reduce the exacerbations of multiple sclerosis. See specification page 4, paragraph [0010]. Thus, Applicant respectfully submits that, to the extent that the Examiner's comments are directed to the role/contribution of IFNAR2 to signal transduction and ligand binding, the full scope of the claims is enabled.

Claims 88 and 89, as amended herein, are directed to the use of a composition comprising the polypeptide of claim 62 to augment the anti-cancer, immune modulating or antiviral properties of IFNβ. Applicants respectfully submit that the full scope of each claim is enabled in view of the present disclosure and the knowledge available to one of ordinary skill in the art at the time of the instant application.

The present disclosure, at Examples 4 and 7 and Figure 4, provides a working example demonstrating enhanced activity of IFN-β/IFNAR2 (wild type and mutant) complexes relative to free IFN-β. In the experiments, the addition of IFNAR2 to a constant amount of IFN-β resulted in a dose-dependent increase in cell survival upon challenge with vesicular stomatitis virus (VSV). Importantly, for its use as a carrier of IFN-β, a significantly lower concentration of the claimed polypeptides is required relative

to the wild type EC, due to the synergistic increase in affinity for IFN-β resulting from the claimed mutations. Contrary to the Examiner's assertion it is irrelevant that "Example 7 is directed to assessment of anti-viral activity and not multiple sclerosis", as these results are applicable to any therapeutic indication in which free IFN-β has shown therapeutic activity, including the claimed anti-cancer and immune modulatory activities. In the context of multiple sclerosis, as noted above, intrathecal administration of IFN-β has been demonstrated to reduce the exacerbations of multiple sclerosis. Accordingly, one of ordinary skill in the art at the time of the instant application would expect that use of the claimed polypeptides as carrier proteins would be effective in treating the disease by augmenting the immune modulatory activity of endogenous IFN-β.

The aforementioned increase in INF-β activity has been demonstrated to occur *in vivo*. European Patent No. EP1037658 B, reference B3 on Form PTO/SB/08A of Applicant's Information Disclosure Statement, mailed February 8, 2005, and considered by the Examiner on November 7, 2005, at Example 11, proves that injection with IFN-β complexed to soluble wild type IFNAR2 enhances the serum half life of IFN-β. Importantly, similar enhancement of the serum half life of IFN-β was observed following an injection of IFN-β followed by a second, separate injection of soluble wild type IFNAR2 (sIFNAR2). **Thus, EP1037658 demonstrates the ability of administered sIFNAR2 to complex *in vivo* with circulating IFN-β.** Moreover, such enhanced half life is demonstrated to result in enhancement and prolongation of IFN-mediated efficacy *in vivo* and such activity would be useful in any disease, such as multiple sclerosis, in which IFN-β itself is active. *See* EP1037658 at Example 14. Importantly, the same ratio as used to maximize the generation of active complex *in vitro* resulted in elongated pharmacokinetics of IFN-β *in vivo*. *See* EP1037658 at page 13, lines 7-9.[1] Accordingly, the instant specification's disclosure that 0.24 nM – 0.4 nM of mutated IFNAR2 polypeptide is optimal for achieving the claimed methods, in view of the aforementioned, provides the guidance necessary to enable the full scope of claims 88 and 89. Adjustments and manipulation of this range may be required depending on a variety of factors such as route of administration, physical characteristics of the individual patient,

[1] Citations to EP1037658 are made with reference to WO 99/32141, an equivalent document.

the extent of symptoms, concurrent treatments and the like. However, such determination of dosage is routine in the art and such adjustments are well within the ability of those skilled in the art

Finally, the Examiner asserts at page 6 of the Office Action that because the "specification also teaches that 'in some inflammatory disorders where it may be required to lower the IFN concentrations, it is possible under certain conditions to use this mutant as an effective antagonist specifically toward IFNβ'" that "it remains unknown whether an administered amount of an IFNAR2 mutant polypeptide would act as a protagonist or antagonist of IFNβ in treating multiple sclerosis." Applicants respectfully submit that this determination is a simple one, well within the ability of one of ordinary skill in the art. EP1037658, page 32, lines 11-17, demonstrates that when soluble IFNAR2 is titrated in at varying concentrations to a given concentration of IFN-β, that enhancement in IFN-β activity is observed up to a maximal IFN-β concentration, **after which IFN-β activity decreased as expected due to competition for IFN-β of the soluble IFNAR2 with the membrane based IFNAR**. Thus, one of ordinary skill in the art would expect that administration of concentrations of IFNAR2 significantly above the optimum concentration for enhancing IFN-β activity *in vitro*, will cause IFNAR2 to act as an antagonist by competing with the membrane bound receptor for IFN-β. This is borne out by Figure 4 of the instant specification (see below).

In view of the foregoing, Applicant respectfully submits that claims 88 and 89 are fully enabled.

2. The Rejections Under 35 U.S.C. §103(a) Should be Withdrawn

a. Claims 62, 66-71 and 75-76

At pages 7-9 of the Office Action, the Examiner maintained the rejection of claims 62, 66-71 and 75-76 under 35 U.S.C. §103(a) over Piehler *et al.* ("Piehler"), which the Examiner characterized as (i) describing the effects of individual mutations at positions His 78 and Asp 100; (ii) providing the motivation to simultaneously mutate His 78 and Asp 100; and (iii) providing a reasonable expectation of success. Applicant respectfully traverses the rejection and requests reconsideration in view of the remarks below.

The instant specification at paragraph [0095], states that "the single mutations in INFAR2 increase the affinity of the complex from 4.6 up to 7.3 fold, while the double mutation [H78A/N100A] causes a synergistic effect" (emphasis added). This is summarized on Table 4 wherein the claimed double mutant H78A/N100A is shown to possess an "above 50-fold" increase in affinity for IFN-β compared to wild type. The single mutant (H78A) possesses only a 4.6-fold increase in affinity for IFN-β over wild type and the single mutant (N100A) possesses only a 7.3-fold increase in affinity for IFN-β over wild type. This is factual evidence and does not constitute attorney argument. Piehler fails to teach or suggest such a result. According to MPEP § 716.02(a), a demonstration of synergy is sufficient to overcome a *prima facie* case of obviousness where the results obtained are greater than those which could have been expected from the prior art to an unobvious extent and the results are of significant, practical advantage.

According to the Examiner, "Piehler et al. specifically describe the mutant H78A as stabilizing the complex with IFN-β nearly two fold; the mutation N100A decreasing the dissociation rate constant for IFN-β by almost four-fold; and further stating: 'It would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2, which should have about a 20-fold tighter binding for IFNβ.'" Therefore, the Examiner alleges, "Piehler expected a synergistic effect for the double mutation." However, the Examiner **has once again** failed to cite the entire sentence from Piehler and therefore **has once again** improperly removed the cited portion from its context. The entire sentence reads:

It would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2, which should have about 20-fold tighter binding for IFNβ **compared to IFNα2**. (emphasis added).

Applicant further directs the Examiner's attention to Piehler et al. at page 230, 1st column, wherein it is taught that the mutant H78A "destabilizes the complex with IFNα2 more than twofold." Thus, it is clear that, when considered in the proper context, the portion of Piehler et al. cited by the Examiner to support the allegation that Piehler et al. expected a synergistic effect for the double mutation, does NOT in fact demonstrate any such expectation. The synergistic increase in affinity recited in the rejected claims, is that of the claimed polypeptide for IFN-β **compared to the wild type polypeptide**. It is this synergism that must be considered during an analysis under 35 U.S.C. § 103 and therefore the only relevant determination with regard to the prior art under this section is the relative affinity of the H78A/N100A mutant for IFNβ compared to wild type IFNAR2, not compared to the affinity of the H78A/N100A mutant for IFNα2, on which the Examiner has improperly founded his determination of obviousness. The proper comparison is made by the instant specification, at page 23, paragraph [0093], which teaches that "the affinity of the IFNAR2 [H78A/N100A] mutant was found to be **approximately 100 times higher** than the wild type towards IFNβ and unchanged towards IFNα2" (emphasis added). Accordingly, the subject matter of the instant claims demonstrate effects greater than those which could have been expected from the prior art to an unobvious extent. The demonstration in the present specification that the affinity of the H78A/N100A mutant for IFNα2 is unchanged relative to wild type protein provides further evidence of the nonobviousness of the double mutant relative to the prior art.

Moreover, the synergism alleged by the Examiner to be expected by Piehler et al. is, according to the Examiner's own statement, "about a 20-fold tighter binding." Notwithstanding the impropriety of the Examiner's analysis, the instant specification discloses that the affinity of the INFAR2 H78A/N100A mutant for IFNβ is about 100-fold higher than that of the wild type polypeptide. Applicant respectfully submits that such a result is greater than that which could have been expected from Piehler et al. to an unobvious extent.

With regard to the Examiner's assertion that "the correlation of thermodynamics with activity is not a one to one relationship and cannot be accurately predicted," Applicants respectfully submit that the term "activity" is not present in the instant claims nor is it relevant to a determination of obviousness thereto. Applicants respectfully submit that the claim term "affinity," known in the art as the reciprocal of the dissociation constant, exhibits a known and precise correlation with free energy of binding. Thus, to whatever extent the Examiner relied on a lack of one-to-one relationship between "activity" and thermodynamics in rejecting the instant claims, the rejections are moot, in view of the known and art-accepted relationship between association rate constant, dissociation rate constant, dissociation constant and free energy of binding.

In light of the unexpected, claimed synergistic increase, no indication of which is disclosed by Piehler and which could not have been obvious to the ordinary artisan, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

b. Claims 77-82

At page 9 of the Final Office Action, the Examiner maintains his rejection of claims 77-81 under 35 U.S.C. §103(a) over Piehler and Campbell *et al.* ("Campbell") and applied this rejection to claim 82 as well. As discussed above, Piehler fails to teach or suggest the synergistic effect of the claimed double mutant H78A/N100A. Campbell, characterized by the Examiner as describing fusion protein constructs containing the hGH signal peptide in place of the native signal sequence of proteins, does nothing to remedy the defect of Piehler. Accordingly, Applicant respectfully requests that the rejection for obviousness be reconsidered and withdrawn.

D. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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